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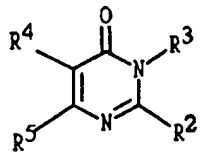
(54) Title: PYRIMIDINONES AS ANTIARTHRITIC AND ANTI-INFLAMMATORIES

(57) Abstract



(I)

Compounds useful in the treatment of inflammation structurally represented as formula (I) or pharmaceutically acceptable salts thereof, wherein R^2 is a) $(CH_2)_n$-Y i) where n is 1 then Y is C_1-C_6 alkoxy, morpholinyl, piperdinyl, pyrrolidinyl, phenoxy, phenylthio, phenylsulfonyl, phenylsulfinyl, -NHC(O)-C_1-C_6 carboxylic acid, N_3, NH_2, diethylamino, hydrogen (provided R^4 is benzyloxy), halogen (provided R^3 is a C_1-C_6 alkyl) or CH("EWG")$_2$ where "EWG" is an electron withdrawing group each individually selected from the group consisting of CO_2R^6 or $PO(OR^7)_2$, or ii) n is 2 then Y is CH("EWG")$_2$, or b) a terminal olefin substituted with i) an aryl or heteroaryl, ii) hydroxyl and a C_1-C_6 alkyl, phenyl or $(CH_2)_m$-CO_2R^6 where m is 1 to 3, or c) C_3-C_6 cycloalkyl (optionally substituted with a halogen, $(PO(OC_2H_5)_2)_2$ or CN); R^3 is hydrogen or C_1-C_6 alkyl; R^4 is hydrogen, hydroxyl, C_1-C_6 alkyl, alkoxy, benzyloxy or phenoxy; R^5 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenoxy, C_1-C_6 alkylthio, thiophenyl, NH_2, aryl (except that R^5 is other than phenyl when R^4 and Y are both hydrogen) or heteroaryl; R^6 is H, C_1-C_6 alkyl, benzyl, phenyl, phenyl substituted with one to five F, Cl, Br, I, NO_2, OCH_3 or C_1-C_4 alkyl; and R^7 is H, C_1-C_6 alkyl, benzyl, phenyl, phenyl substituted with one to five F, Cl, Br, I, NO_2, OCH_3 or C_1-C_4 alkyl, or where both R^7's are taken together to form a CH_2-CH_2, CH_2-CH_2-CH_2 or CH_2-$C(CH_3)_2$-CH_2 whereby a heterocyclic ring containing the bonded P atom and the two O atoms is formed. The compounds are useful as anti-inflammatory and antiarthritic agents.

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PYRIMIDINONES AS ANTIARTHRITIC AND ANTI-INFLAMMATORIES

BACKGROUND OF THE INVENTION

The present invention is directed toward pyrimidinones and their pharmaceutically acceptable salts which are characterized by (Formula I) which are useful as anti-inflammatories and antiarthritic agents.

The present compounds are useful in humans and lower animals as a safe and effective treatment of chronic inflammatory diseases. These diseases include periodontal disease, rheumatoid arthritis, osteoarthritis, neuritis, bursitis, pneumoconioses, Crohn's disease, chronic inflammatory bowel disease, chronic asthma, atherosclerosis, multiple sclerosis, and sarcoidosis.

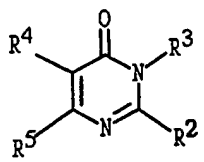
DESCRIPTION OF THE RELATED ART

For state of the art purposes, US Patent 4,746,654 discloses bisphosphonates useful as anti-inflammatory agents; Australian Patent A-51534/85 discloses bisphosphonates useful in treating abnormal calcium and phosphorous metabolism and useful in treating arthritis; and US Patent 3,683,080 discloses polyphosphonates; in particular, diphosphonates useful in inhibiting anomalous deposition and mobilization of calcium phosphate in animal tissue.

European Patent Application 0 168 262 discloses an intermediate pyrimidine compound, Formula VIIa which is similar to the subject compound except that the corresponding R_2 is only hydrogen or a lower alkyl. The compounds are described to be useful for treating hypertension and cerebrovascular disease.

SUMMARY OF THE INVENTION

In one aspect, the present invention is pyrimidinones or its pharmaceutically acceptable salts which are structurally represented by Formula I



wherein R^2 is a) $(CH_2)_n$-Y and

i) where n is 1 then Y is C_1-C_6 alkoxy, morpholinyl, piperdinyl,

pyrrolidinyl, phenoxy, phenylthio, phenylsulfonyl, phenylsulfinyl, -NHC(O)-C_1-C_6 carboxylic acid, N_3, NH_2, diethylamino, hydrogen (provided R^4 is benzyloxy), halogen (provided R^3 is a C_1-C_6 alkyl) or CH("EWG")$_2$ where "EWG" is an electron withdrawing group each individually selected from the group consisting of CO_2R^6 or $PO(OR^7)_2$, or

ii) where n is 2 then Y is CH("EWG")$_2$, or

b) a terminal olefin substituted with

i) an Aryl or Heteroaryl,

ii) hydroxyl and a C_1-C_6 alkyl, phenyl or $(CH_2)_m$-CO_2R^6 where m is 1 to 3, or

c) C_3-C_6 cycloalkyl (optionally substituted with a halogen, $(PO(OC_2H_5)_2)_2$ or CN;

R^3 is hydrogen or C_1-C_6 alkyl;

R^4 is hydrogen, hydroxyl, C_1-C_6 alkyl, alkoxy, benzyloxy or phenoxy;

R^5 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenoxy, C_1-C_6 alkylthio, thiophenyl, NH_2, Aryl (except that R^5 is other than phenyl when R^4 and Y are both hydrogen) or Heteroaryl;

R^6 is H, C_1-C_6 alkyl, benzyl, phenyl, phenyl substituted with one to five F, Cl, Br, I, NO_2, OCH_3 or C_1-C_4 alkyl; and

R^7 is H, C_1-C_6 alkyl, benzyl, phenyl, phenyl substituted with one to five F, Cl, Br, I, NO_2, OCH_3 or C_1-C_4 alkyl, or where both R^7's are taken together to form a CH_2-CH_2, CH_2-CH_2-CH_2 or CH_2-$C(CH_3)_2$-CH_2 whereby a heterocyclic ring containing the bonded P atom and the two O atoms is formed.

In another aspect, the present invention comprises the use of these compounds in humans and lower animals as a safe and effective treatment of chronic inflammatory diseases. These diseases include periodontal disease, rheumatoid arthritis, osteoarthritis, pneumoconioses, Crohn's disease, chronic inflammatory bowel disease, chronic asthma, atherosclerosis, multiple sclerosis, and sarcoidosis.

In yet another aspect, the invention is a method for treating inflammation by administering to a patient (animals, including humans) in need of such treatment an anti-inflammatory effective amount of a compound of Formula I. Routes of administration include oral, intramuscular, intravenous, transdermal, intra-articular, subcutaneous, or intraperitoneal. An effective amount is an amount whereby the symptoms of inflammation or arthritis such as pain and discomfort are relieved or reduced or mobility of the affected area is increased. A typical dosage is about 0.001

mg to 1.0 gram with dose determined by the particular mode of administration, use and frequency of administration.

DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises pyrimidinones and their pharmaceutically acceptable salts which are characterized by (Formula I, above) and which are useful as anti-inflammatories and anti-arthritic agents. These compounds are particularly useful in the treatment of arthritis and its associated symptoms such as inflammation and excessive bone growth or remodelling. In Formula I, the variable designations are further defined as follows.

The carbon content of various hydrocarbon containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_i-C_j defines the number of carbon atoms present from the integer "i" to the integer "j" inclusive. Thus, C_1-C_3 alkyl refers to alkyl of 1-3 carbon atoms, inclusive, or methyl, ethyl, propyl, and isopropyl.

With respect to the above, C_1-C_6 alkyl is methyl, ethyl, propyl, butyl, pentyl, hexyl, and isomeric forms thereof. "Aryl" means phenyl or naphthyl. "Heteroaryl" means morpholinyl, piperazinyl, piperidinyl, imidazolidinyl, pyrazolidinyl, isoxazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl or pyridazinyl. The term "halogen" includes fluoro, chloro, bromo and iodo. "Terminal olefin" means $-CH=CH_2$ which can then have one or both of the terminal hydrogens substituted as indicated.

Pharmaceutically acceptable salts means salts useful for administering the compounds of this invention or useful forms the compounds may take *in vitro* or *in vivo* and include potassium, sodium, hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, mesylate, maleate, malonate, succinate, tartrate, citric acid and the like. These salts may be in hydrated form.

The pyrimidinones and derivatives (Formula I) useful as anti-inflammatories and antiarthritics are prepared as shown in Examples 1-35 and in Table 1, below.

The Formula I compounds of this invention have been tested in a Delayed Type Hypersensitivity Granuloma Assay (DTH GRA) model for inflammation. This assay is described by Dunn, C. J. et al., "Development of a delayed-type hypersensitivity granuloma model in the mouse for the study of chronic immune-mediated inflammatory disease," Agents and Actions, 27, 3/4 (1989) and "Murine Delayed-Type Hypersensitivity Granuloma," Int. J. Immunopharmc., 12, 8:899-904 (1990).

Briefly, mBSA-sensitized mice have a DTH granuloma (DTH GRA) lesion induced by subcutaneously implanting a mBSA-soaked filter which is excised after nine

days. Compounds are administered to the mice to determine their effect on the lesions. The results are recorded as percent inhibition. The larger the inhibition, the more effective the compound. Inhibition of 10 to 20% is considered to indicate anti-granuloma activity. Greater than 30% inhibition is good activity. The DTH GRA data obtained from the compounds of Formula 1 are shown in the Table 2, below. The compounds are scored as having anti-inflammatory activity at 10-20% inhibition and good activity at greater than 30% inhibition.

The "compound designations" correspond to the Examples' designations. The particular compounds designated are as follows:

TABLE 1

EXAMPLE	R^2	R^3	R^4	R^5
1	$-CH_2-Cl$	CH_3	H	Ph
2	$-CH_2-O-Ph$	CH_3	H	Ph
3	$-CH_2-S-Ph$	CH_3	H	Ph
4	$-CH_2-CH(PO(OEt)_2)_2$	CH_3	H	Ph
5	$-CH_2-CH(CO_2Et)_2$	CH_3	H	Ph
6	$-CH_2-CH(CO_2Et)\ (PO(OEt)_2)$	CH_3	H	Ph
7	$-CH_2$-morpholinyl	CH_3	H	Ph
8	$-CH_2$-piperidinyl	CH_3	H	Ph
9	$-CH_2$-pyrrolidinyl	CH_3	H	Ph
10	$-CH_2$-diethylamino	CH_3	H	Ph
11	$-CH_2-OCH_3$	CH_3	H	Ph
12	$-CH_2-N_3$	CH_3	H	Ph
13	$-CH_2-I$	CH_3	H	Ph
14	$-CH_2-NH_2$	CH_3	H	Ph
15	$-CH_2-NH-C(O)(CH_2)_2-COOH$	CH_3	H	Ph
16	$-CH_2-NHC(O)-(CH_2)_3-COOH$	CH_3	H	Ph
17	$-CH_2-SO_2-Ph$	CH_3	H	Ph
18	$-CH_2-S(O)-Ph$	CH_3	H	Ph
19	$-CH=C(OH)-(CH_2)_2-COOH$	CH_3	H	Ph
20	$-CH=C(OH)-(CH_2)_3-COOH$	CH_3	H	Ph
21	$-CH=C(OH)-(CH_2)_2-COOCH_3$	CH_3	H	Ph
22	$-(c-C_3H_3)-(PO(OC_2H_5)_2)_2$	CH_3	H	Ph

EXAMPLE	R^2	R^3	R^4	R^5
23	-(c-C_3H_4)trans-CN	CH_3	H	Ph
24	-(c-C_3H_4)cis-CN	CH_3	H	Ph
25	-$(CH_2)_2$-CH(COO-tBu)$_2$	CH_3	H	Ph
26	-CH_3	CH_3	-O-CH_2-Ph	Ph
27	-$(CH_2)_2$-CH(PO(OEt)$_2$)$_2$	CH_3	-O-CH_2-Ph	Ph
28	-$(CH_2)_2$-CH(PO(OEt)$_2$)$_2$	CH_3	-OH	Ph
29*	-CH_3	CH_3	H	-Cl
30*	-CH_3	CH_3	H	-O-CH_3
31*	-CH_3	CH_3	H	-S-Ph
32*	-CH_3	CH_3	H	piperidine
33	-$(CH_2)_2$-CH(PO(OEt)$_2$)$_2$	CH_3	H	Cl
34	-$(CH_2)_2$-CH(PO(OEt)$_2$)$_2$	CH_3	H	-S-Ph
35	-$(CH_2)_2$-CH(PO(OEt)$_2$)$_2$	CH_3	H	piperidine

* Not compounds of the invention.

TABLE 2

Example	Dose (mpk)	% Inhibition Wet Weight	% Inhibition Dry Weight
1	10	47	54
2	10	28	37
3	10	21	30
4	10	31	35
5	10	51	53
7	10	64	68
12	10	39	48
15	10	64	60
16	10	52	52
17	10	20	24
18	10	26	26
19	10		46
20	10	20	28
21	10	35	43
22	10	10	28
23	10	22	24
24	10	27	24
25	10	51	40
26	10	71	60
28	10	57	46

EXAMPLE 1: 4(3H)-Pyrimidinone, 2-(chloromethyl)-3-methyl-6-phenyl-

Procedure A:

4(3H)-Pyrimidinone, 2,3-dimethyl-6-phenyl (11.0 g, 54.9 mmol) in THF (55 ml) was added slowly to a -78°C solution of LiHMDS (1M in THF, 60 ml, 60 mmol). After stirring for 45 minutes, this was then cannulated into a -40°C solution of hexachloroethane (13.64 g, 57.6 mmol) in THF (50 ml) over a period of 45 minutes. The reaction was warmed to room temperature for 1 hour, then quenched with NH_4Cl, extracted thrice with ethyl acetate, washed with saturated $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated *in vacuo*. The product was recrystallized from methyl

t-butyl ether: 6.555 g (27.9 mmol, 51%), mp 121-122°C.

EXAMPLE 2: 4(3H)-Pyrimidinone, 3-methyl-2-(phenoxymethyl)-6-phenyl-

Procedure B:

To a 0°C suspension of sodium hydride (0.191 g, 3.98 mmol) in toluene (9 ml) was added phenol (0.34 g, 3.61 mmol). After 15 minutes, 2-(chloromethyl)-3-methyl-6-phenyl-4(3H)- pyrimidinone (0.775 g, 3.2 mmol) was added and the reaction heated to reflux for 2.5 hours. After cooling, the reaction mixture was diluted with methylene chloride, then washed thrice with saturated $NaHCO_3$, dried with $MgSO_4$ and concentrated *in vacuo* (57%), mp 104-105°C.

Made by the same method of Example 2 were Examples 3-6, whose compounds are identified below.

EXAMPLE 3: 4(3H)-Pyrimidinone, 3-methyl-6-phenyl-2-[(phenylthio)methyl]-

The compound of Formula I where R^3 is methyl; R^4 is hydrogen; R^5 is phenyl; and R^2 is $-CH_2$-S-Phenyl, mp 94-95°C.

EXAMPLE 4: Phosphonic acid, [2-(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl) ethylidene]bis-, tetraethyl ester

The compound of Formula I where R^3 is methyl; R^4 is hydrogen; R^5 is phenyl; and R^2 is $-CH_2-CH-(PO(OEt)_2)_2$, mp 86-88°C.

EXAMPLE 5: Propanedioic acid, [(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)methyl]-, diethyl ester

The compound of Formula I where R^3 is methyl; R^4 is hydrogen; R^5 is phenyl; and R^2 is $-CH_2-CH-(CO_2Et)_2$, mp 102-103°C.

EXAMPLE 6: 2-Pyrimidinepropanoic acid, .alpha.-(diethoxyphosphinyl)-1,6-dihydro-1- methyl-6-oxo-4-phenyl-, ethyl ester

The compound of Formula I where R^3 is methyl; R^4 is hydrogen; R^5 is phenyl; and R^2 is $-CH_2-CH(CO_2Et)(PO(OEt)_2)$, mp 119°C.

EXAMPLE 7: 4(3H)-Pyrimidinone, 3-methyl-2-(4-morpholinylmethyl)-6-phenyl-

Procedure C:

2-(chloromethyl)-3-methyl-6-phenyl-4(3H)-pyrimidinone (0.507 g, 2.2 mmol) in

THF (12 ml) was treated with morpholine (0.40 ml, 4.5 mmol), then heated to reflux for 1.5 hours. The reaction mixture was cooled, filtered through a pad of Celite, and concentrated *in vacuo*. The residue was dissolved in methylene chloride and filtered a second time. The organic layer was concentrated *in vacuo* to provide a light yellow solid. Crude material was purified by recrystallization from ethyl acetate (27%), mp 135-136°C.

EXAMPLE 8: 4(3H)-Pyrimidinone, 3-methyl-6-phenyl-2-piperidinyl-

Made by the same method of Example 7, the title compound was prepared, mp 133-134°C.

EXAMPLE 9: 4(3H)-Pyrimidinone, 3-methyl-6-phenyl-2-pyrrolidinyl-

Made by the same method of Example 7, the title compound was prepared, mp 112-113°C.

EXAMPLE 10: 4(3H)-Pyrimidinone, 2-dimethylamino-3-methyl-6-phenyl-

Made by the same method of Example 7, the title compound was prepared, mp 84-85°C.

EXAMPLE 11: 4(3H)-Pyrimidinone, 2-methoxy-3-methyl-6-phenyl-

Made by the same method of Example 7, the title compound was prepared, mp 86-87°C.

EXAMPLE 12: 4(3H)-Pyrimidinone, 2-(aziodomethyl)-3-methyl-6-phenyl-

4(3H)-Pyrimidinone, 2-(iodomethyl)-3-methyl-6-phenyl- (4.06 g, 12.4 mmol) was treated with sodium azide (1.62 g, 24.9 mmol) and acetonitrile (25 ml) and stirred at 22°C for 60 hours then concentrated *in vacuo*. The residue was dissolved in methylene chloride, washed with saturated $NaHCO_3$, 3x 1M $NaHSO_3$, saturated NaCl, dried with $MgSO_4$, and concentrated *in vacuo* (40%), mp 111-112°C.

EXAMPLE 13: 4(3H)-Pyrimidinone, 2-(iodomethyl)-3-methyl-6-phenyl-

2-(chloromethyl)-3-methyl-6-phenyl-4(3H)-pyrimidinone (0.98 g, 4.16 mmol) and sodium iodide (0.654 g, 4.37 mmol) were combined in acetone (10 ml) and heated to reflux for 30 minutes. The reaction mixture was cooled, filtered and concentrated *in vacuo*. The resulting solid was dried under high vacuum to recover a bright yellow solid.

EXAMPLE 14: 4(3H)-Pyrimidinone, 2-(aminomethyl)-3-methyl-6-phenyl-

2-(chloromethyl)-3-methyl-6-phenyl-4(3H)-pyrimidinone (3.98 g, 17.0 mmol) and sodium azide (2.21 g, 34 mmol) were combined in acetonitrile (25 ml) and heated to a gentle reflux for 1 hour. After cooling to room temperature, the solvent was removed *in vacuo*. The residues were diluted with methylene chloride and washed with 6% $NaHCO_3$, H_2O, and brine, treated with charcoal and filtered through a pad of $MgSO_4$. After concentration *in vacuo*, the crude product was resuspended in a mixture of ethanol (80 ml) with 5% palladium on carbon (0.4 g) and hydrogenated in an atmosphere of hydrogen for 2 hours. The reaction mixture was filtered through Celite and concentrated *in vacuo*. The product was recrystallized from ethyl acetate/hexane: 0.80 g (3.7 mmol, 22%), mp 90-92°C.

EXAMPLE 15: Butanoic acid, 4-[[(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl) methyl]amino]-4-oxo-

4(3H)-Pyrimidinone, 2-(aminomethyl)-3-methyl-6-phenyl- (304 mg, 1.41 mmol) dissolved in chloroform (5 ml) was treated with succinic anhydride (141 mg, 1.41 mmol) then heated to reflux for 1 hour. The resultant solid was filtered, washed with chloroform and dried: 0.377 g, (1.20 mmol, 85%), mp 200-201°C.

EXAMPLE 16: Pentanoic acid, 5-[[(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl) methyl]amino]-5-oxo-

In a similar to Example 15 manner the title compound was prepared: from glutaric anhydride (62%), mp 181-182°C.

EXAMPLE 17: 4(3H)-Pyrimidinone, 3-methyl-6-phenyl-2-[(phenylsulfonyl)-methyl]-

Benzenesulfinic acid, sodium salt (0.346 g, 2.1 mmol) was slurried in toluene (5 ml), then treated with 4(3H)-Pyrimidinone, 2-(iodomethyl)-3-methyl-6-phenyl- (0.517 g, 1.6 mmol) and heated to 70°C for 20 hours. The reaction was cooled to room temperature and most of the solvent was removed *in vacuo*. The residue was dissolved in methylene chloride, washed thrice with saturated $NaHCO_3$ and 1M $NaHSO_3$, dried with $MgSO_4$, and concentrated *in vacuo*. The product was purified by chromatography on silica gel: 226 mg (0.66 mmol, 41%), mp 174-175°C.

EXAMPLE 18: 4(3H)-Pyrimidinone, 3-methyl-6-phenyl-2-[(phenylsulfinyl)-methyl]-

4(3H)-Pyrimidinone, 3-methyl-6-phenyl-2-[(phenylthio)methyl]- (0.589 g, 1.91 mmol) dissolved in methanol (10 ml) at 0°C was treated with an aqueous solution of oxone (7.23 g, 5.7 mmol) in water (21 ml). The reaction mixture was stirred at 0°C for 5 hours, then treated with 1M $NaHSO_3$ and concentrated *in vacuo* while heating the sample to 40°C. Methylene chloride was added and after separation, the organic layer was washed 3x 1M $NaHSO_3$, saturated $NaHCO_3$, dried with $MgSO_4$ and concentrated *in vacuo*. The sample was purified by chromatography on silica gel: 217 mg (0.67 mmol, 35%), mp 158-159°C.

EXAMPLE 19: 4-Pentenoic acid, 5-(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)-4-hydroxy-, (Z)-

4(3H)-Pyrimidinone, 2,3-dimethyl-6-phenyl (5.45 g, 27.2 mmol) was dissolved in THF (25 ml), cooled to -20°C, and treated with LiHMDS (1M in THF, 60 ml, 60 mmol). After stirring for 30 minutes, succinic anhydride (3.0 g, 30.0 mmol) was added and the reaction warmed to room temperature for 2 hours. It was quenched with water, extracted twice with ethyl acetate, and the aqueous solution was acidified with 1N HCl then filtered. The product was recrystallized from iPrOH: 4.30 g (14.3 mmol, 53%), mp 232-233°C.

EXAMPLE 20: 5-Hexenoic acid, 6-(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)-5-hydroxy-, (Z)-

In a similar manner to Example 19, title compound was prepared from glutaric anhydride (26%), mp 170-171°C.

EXAMPLE 21: 4-Pentenoic acid, 5-(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)-4-hydroxy-, methyl ester, (Z)-

4-Pentanoic acid, 5-(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)-4-hydroxy-, (Z)-(693 mg, 2.31 mmol) in methanol (25 ml) and H_2SO_4 (1 drp) was heated to reflux for 3 hours. After removing the bulk of the methanol *in vacuo*, the crystals were filtered and washed with ether: 646 mg (2.06 mmol, 89%), mp 153°C.

EXAMPLE 22: Phosphonic acid, [(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)cyclopropylidene]bis-,tetraethyl ester

4(3H)-Pyrimidinone, 2-(chloromethyl)-3-methyl-6-phenyl- (705 mg, 3.0 mmol), ethenylidenebis(phosphonic acid), tetraethyl ester (900 mg, 3.0 mmol) and DBU (0.5 ml,

3.3 mmol) were stirred in THF(5 ml) at room temperature for 24 hours. The reaction was quenched with NH_4Cl, extracted thrice with ethyl acetate, dried with $MgSO_4$, and stripped. The crude was purified by silica gel chromatography: 471 mg (0.95 mmol, 32%), NMR: δ ($CDCl_3$) 7.97 (m, 2H), 7.44 (m, 3H), 6.84 (s, 1H), 4.39 (m, 4H), 4.1-3.8 (m, 4H), 3.75 (s, 3H), 2.99 (m, 1H), 2.56 (m, 1H), 1.95 (m, 1H), 1.402 (t, J=7.2, 3H), 1.39 (t, J=7.2, 3H), 1.19 (t, J=7.2, 3H), 1.08 (t, J=7.2, 3H).

EXAMPLE 23: Cyclopropanecarbonitrile, 2-(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)-, trans-

By the same method in Example 22, the title compound was prepared, mp 166-167°C.

EXAMPLE 24: Cyclopropanecarbonitrile, 2-(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)-, cis-

By the same method in Example 22, the title compound was prepared, mp 195-196°C.

EXAMPLE 25: Propanedioic acid, [2-(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)ethyl]-, bis(1,1-dimethylethyl) ester

4(3H)-Pyrimidinone, 2,3-dimethyl-6-phenyl (0.744 g, 3.72 mmol) was dissolved in THF (37 ml), cooled to -78°C, then treated with lithium bis(trimethylsilyl)amide (4.1 ml, 4.1 mmol). After stirring for 30 minutes at -78°C, a solution of 2-t-butylcarboxy-2-propenoic acid t-butyl ester (0.424 g, 1.86 mmol) in THF (10 ml) was added slowly over approximately 1 hour using a syringe pump. The reaction was quenched immediately with 4.1M NH_4Cl (1 ml, 4.1 mmol) then warmed to 22°C. The reaction mixture was concentrated *in vacuo* and dissolved in ethyl acetate. The organic layer was washed 3x 1N HCl, H_2O, 3x $NaHCO_3$ and brine, then dried with $MgSO_4$ and concentrated *in vacuo*. The crude mixture was chromatographed on silica gel: 0.317 g (0.74 mmol, 40%), mp 94-95°C.

EXAMPLE 26: 4(3H)-Pyrimidinone,2,3-dimethyl-6-phenyl-5-(phenylmethoxy)-

Sodium hydride (50% in oil, 19.2 g, 0.40 mol) was suspended in toluene (200 ml), then benzyl alcohol (43.2 g, 0.40 mol) was added dropwise. After stirring for 45 minutes, the gray foam was treated slowly with a solution of chloroacetic acid (18.8 g, 0.20 mol) in toluene (100 ml), then heated to reflux. After refluxing for 2 hours, the reaction was cooled to room temperature and poured onto water (100 ml). The organics

were separated and the toluene extracted twice with water. The aqueous layer was washed with methyl t-butyl ether and the organics discarded. After adjusting the pH to 2 with concentrated HCl, the aqueous fraction was extracted thrice with methylene chloride, dried with $MgSO_4$, and concentrated *in vacuo*: 29.50 g. This crude material, ethanol (40 ml), toluene (50 ml), and concentrated H_2SO_4 (3 ml) were heated to reflux overnight. After cooling, it was washed with water, $NaHCO_3$, dried with $MgSO_4$, and concentrated *in vacuo*. The product was isolated by distillation: 24.38 g (0.126 mol, 63%) $Bp_{0.1}$ 55-60°C. This synthesis is essentially identical to that described in *Aust. J. Chem.* **1976**, *29*, 1335-1339.

The ester (22.10 g, 0.113 mol) was dissolved in THF (5 ml) and added slowly to a -78°C solution of LiHMDS (1 M in THF, 230 ml, 0.230 mol). After stirring for 45 minutes, benzoyl chloride (13.1 ml, 0.113 mol) was added and the reaction warmed to room temperature for 45 minutes. It was quenched with 1 N HCl, extracted thrice with methyl t-butyl ether, dried with $MgSO_4$, and stripped: 45.68 g (0.153 mol). The crude material, acetamidine hydrochloride (28.95 g, 0.306 mol), and 25% sodium methoxide/methanol (77 ml, 0.336 mol) were combined and heated to reflux for 36 hours. It was cooled, diluted with water, and pH adjusted to 7 with concentrated HCl. The precipitate was collected, washed with cold ether, and air dried: 20.45 g (70.00 mmol, 62%), mp 168°C.

The pyrimidinone (5.84 g, 20.0 mmol), K_2CO_3 (3.20 g, 23 mmol), and methyl iodide (3.7 ml, 60 mmol) were heated in refluxing methanol (50 ml) overnight. The reaction was cooled and seeded. The precipitate was collected, washed with water and dried in the oven: 5.052 g (16.49 mmol, 82%), mp 118-119°C.

EXAMPLE 27: Phosphonic acid, [3-[1,6-dihydro-1-methyl-6-oxo-4-phenyl-5-(phenylmethoxy)-2-pyrimidinyl]propylidene]bis-, tetraethyl ester

To a -78°C solution of LiHMDS (1 M in THF, 8.4 ml, 8.4 mmol) was added a solution of 4(3H)-Pyrimidinone, 2,3-dimethyl-6-phenyl-5-(phenylmethoxy)- (1.23 g, 4.0 mmol) in THF/pyridine (1:1, 4 ml). After stirring for 30 minutes, ethenylidenebis(phosphonic acid), tetraethyl ester (2.52 g, 8.4 mmol) in THF (5 ml) was added and the reaction warmed to room temperature for 30 minutes. It was quenched with water, extracted thrice with ethyl acetate, washed once with 1N HCl, $NaHCO_3$, and brine, then dried with $MgSO_4$, and stripped. The sample was purified by silica gel chromatography: 1.937 g (3.19 mmol, 80%), NMR: δ ($CDCl_3$) 8.04 (m, 2H), 7.38 (m, 3H), 7.31 (m, 2H), 7.25 (m, 3H), 5.08 (s, 2H), 4.17 (m, 8H), 3.60 (s, 3H), 3.13 (t, J=7.2, 2H),

2.79 (tt, J_{t1}=6.6, J_{t2}=23.7, 1H), 2.46 (m, 2H), 1.32 (m, 12H).

EXAMPLE 28: Phosphonic acid, [3-(1,6-dihydro-5-hydroxy-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)propylidene]bis-, tetraethyl ester

Phosphonic acid, [3-[1,6-dihydro-1-methyl-6-oxo-4-phenyl-5-(phenylmethoxy)-2-pyrimidinyl]propylidene]bis-, tetraethyl ester (1.60 g, 2.64 mmol) in ethanol (50 ml) was treated with 10% Pd/C (320 mg) and ammonium formate (4.00 g), then heated to reflux for 2 hours. The catalyst was removed by filtering through Celite and stripped. The residue was dissolved in methylene chloride, filtered through a short pad of silica gel and the pad was washed well with acetone. After concentration, the crude material was recrystallized from methyl t-butyl ether: 884 mg (1.71 mmol, 65%), mp 138-139°C.

EXAMPLE 29: 4(3H)-Pyrimidinone, 6-chloro-2,3-dimethyl-

Hydrogen chloride gas (2.0 g, 55 mmol) was slowly bubbled into acetonitrile (7.5 ml). A second solution containing phosgene (4.9 g, 50 mmol) in acetonitrile (7.5 ml) was prepared in a pressure bottle and the HCl solution was added to the pressure bottle. The mixture was stoppered tightly and heated to 60-65°C for 64 hours. The solution was cooled to -78°C and filtered, then the solid was washed with a small amount of acetonitrile followed by washing with hexanes: 4.06 g (22.4 mmol, 45%).

6-chloro-2-methyl-4-pyrimidinone • HCl (3.95 g, 21.7 mmol) and potassium carbonate (8.98 g, 65 mmol) were slurried in acetone (90 ml), iodomethane (3.4 ml, 54.2 mmol) was added and the solution refluxed for 2 hours. The reaction mixture was cooled and concentrated *in vacuo*. The residue was dissolved in methylene chloride and washed with saturated NH_4Cl, dried with $MgSO_4$ and concentrated *in vacuo*: 3.3 g (20.8 mmol, 96%), mp 85-86°C.

EXAMPLE 30: 4(3H)-Pyrimidinone, 2,3-dimethyl-6-methoxy-

Diethyl malonate (28.6 g, 0.178 mol) was dissolved in methanol (180 ml) and acetamidine • HCl added. The suspension was treated with 25% sodium methoxide in methanol (86 ml, 0.375 mol), heated to reflux for 3.5 hours, then cooled and diluted with sufficient H_2O to dissolve the solids. The solution was cooled to 0°C and neutralized with concentrated HCl to pH 6.5-6.0. The thick solid was filtered and dried on the filter to provide 14.1 g of crude material which was used directly in the next reaction. Compound is described in *Collect. Czech. Chem. Commun.*, *32*:1298-304 (1967).

The intermediate 6-hydroxy-2-methyl-4-pyrimidinone • HCl (14.1 g, 0.11 mol)

was slurried in methanol (160 ml) and treated with potassium carbonate (46.3 g, 0.33 mol) and iodomethane (28 ml, 0.45 mol), then heated to reflux for 45 hours. After cooling and concentration *in vacuo*, the residue was dissolved in H_2O and washed 6 x with methylene chloride. The combined organics were concentrated *in vacuo* and the yellow oil solidified upon standing. Recrystallized from toluene /cyclohexane to recover an off-white solid which appeared to be slightly hygroscopic, 12.1 g, (67 mmol, 37%), mp 66-68°C.

EXAMPLE 31: 4(3H)-Pyrimidinone,2,3-dimethyl-6-phenylthio-

Sodium hydride (0.36 g, 7.5 mmol) slurried in dimethyl formamide (25 ml) was treated with thiophenol (0.73 ml, 7.12 mmol) and 6-chloro-2,3-dimethyl-4(3H)-pyrimidinone (1.13 g, 7.13 mmol). The mixture was stirred at 22°C for 24 hours then diluted with H_2O (70 ml). The aqueous solution was washed with ethyl acetate (50 ml) and after separation, hexane (50 ml) was added to the organic layer. The combined organics were washed 5 x H_2O and brine, dried with $MgSO_4$, then concentrated *in vacuo*. The pale yellow solid 4(3H)-Pyrimidinone,2,3-dimethyl- 6-phenylthio- was recrystallized from methyl t-butyl ether: 0.87 g (3.7 mmol, 53%), mp 105-106°C.

EXAMPLE 32: 4(3H)-Pyrimidinone, 2,3-dimethyl-6-piperidinyl

4(3H)-Pyrimidinone, 6-chloro-2,3-dimethyl- (0.778 g, 4.90 mmol) was slurried in piperidine (15 ml) and the solution was heated to reflux for 1 hour, then at 60°C for 18 hours. The reaction mixture was filtered through Celite and concentrated *in vacuo*. The residue was dissolved in methylene chloride and washed with 6% $NaHCO_3$, 2 x H_2O, then dried with $MgSO_4$. The solvent was concentrated *in vacuo* and the orange oil was chromatographed on SiO_2 with 10:1 ethyl acetate /methanol. The material 4(3H)-Pyrimidinone, 2,3-dimethyl-6-piperidinyl- recovered from the column was recrystallized from methyl t-butyl ether to provide 0.64 g, (3.1 mmol, 63%) of light brown crystals, mp 97-98°C.

EXAMPLE 33: 3-(1,6-Dihydro-4-chloro-1-methyl-6-oxo-2-pyrimidinyl)-propylidene bisphosphonic acid, tetraethyl ester

4(3H)-Pyrimidinone, 6-chloro-2,3-dimethyl- (3.25 g, 20.5 mmol) dissolved in THF (40 ml) was cooled to -78°C and treated with LiHMDS (21.5 ml, 21.5 mmol) and stirred for 1 hour. A solution of ethenylidenebis(phosphonic acid), tetraethyl ester (5.84 g, 19.5 mmol) in THF (10 ml) was added slowly and after 30 minutes at -78°C, the reaction mixture was warmed to 0°C for one hour. The reaction was quenched with saturated

NH_4Cl and concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed 3 x with saturated NH_4Cl, 3 x saturated $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude material 3-(1,6-Dihydro-4-chloro-1-methyl-6-oxo-2-pyrimidinyl)-propylidene bisphosphonic acid, tetraethyl ester was purified by chromatography on silica gel: 7.1 g (15.5 mmol, 79%) NMR: δ ($CDCl_3$) 6.35 (s, 1H), 4.20-4.04 (m, 8H), 3.47 (s, 3H), 3.08 (t, J=7.3, 2H), 2.62 (tt, J_{t1}=6.6, J_{t2}=23.8, 1H), 2.43-2.25 (m, 2H), 1.29 (t, J=7.0, 12H).

EXAMPLE 34: 3-(1,6-Dihydro-1-methyl-6-oxo-4-phenylthio-2-pyrimidinyl)-propylidene bisphosphonic acid, tetraethyl ester

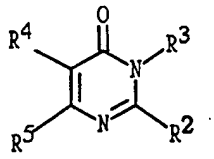
In a similar manner the title compound was prepared from 4(3H)-Pyrimidinone, 2,3-dimethyl-6-phenylthio-: (88%), NMR: δ ($CDCl_3$) 7.58-7.55 (m, 2H), 7.48-7.43 (m, 3H), 5.67 (s, 1H), 4.28-4.16 (dq, 8H), 3.47 (s, 3H), 3.10 (t, J=7.3, 2H), 2.72 (tt, J_{t1}=6.4, J_{t2}=24, 1H), 2.47-2.33 (m, 2H), 1.37 (t, J=7.0, 12H).

EXAMPLE 35: 3-(1,6-Dihydro-1-methyl-6-oxo-4-piperidinyl-2-pyrimidinyl)-propylidene bisphosphonic acid, tetraethyl ester

3-(1,6-Dihydro-4-chloro-1-methyl-6-oxo-2-pyrimidinyl)-propylidene bisphosphonic acid, tetraethyl ester (from Ex. 33) (1.17 g, 2.56 mmol) was added to piperidine (8 ml) and the solution was heated gently to 50-60°C for 2 hours. The solution was cooled and filtered through Celite and concentrated *in vacuo*. The resultant oil was chromatographed on SiO_2: 0.83 g (1.63 mmol, 64%), NMR: δ ($CDCl_3$) 5.40 (s, 1H), 4.24-4.14 (m, 8H), 3.53-3.50 (m, 4H), 3.44 (s, 3H), 3.00 (t, J=7.3, 2H), 2.72 (tt, J_{t1}=6.7, J_{t2}=24, 1H), 2.49-2.34 (m, 2H), 1.68-1.57 (m, 6H), 1.34 (m, 12H).

WHAT IS CLAIMED

1. A compound of Formula I or pharmaceutically acceptable salts thereof wherein Formula I is



wherein R^2 is a) $(CH_2)_n$-Y

i) where n is 1 then Y is C_1-C_6 alkoxy, morpholinyl, piperdinyl, pyrrolidinyl, phenoxy, phenylthio, phenylsulfonyl, phenylsulfinyl, -NHC(O)-C_1-C_6 carboxylic acid, N_3, NH_2, diethylamino, hydrogen (provided R^4 is benzyloxy), halogen (provided R^3 is a C_1-C_6 alkyl) or CH("EWG")$_2$ where "EWG" is an electron withdrawing group each individually selected from the group consisting of CO_2R^6 or $PO(OR^7)_2$, or

ii) where n is 2 then Y is CH("EWG")$_2$,

b) a terminal olefin substituted with

i) an Aryl or Heteroaryl,

ii) hydroxyl and an C_1-C_6 alkyl, phenyl or $(CH_2)_m$-CO_2R^6 where m is 1 to 3, or

c) C_3-C_6 cycloalkyl (optionally substituted with a halogen, $(PO(OC_2H_5)_2)_2$ or CN);

R^3 is hydrogen or C_1-C_6 alkyl;

R^4 is hydrogen, hydroxyl, C_1-C_6 alkyl, alkoxy, benzyloxy or phenoxy;

R^5 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenoxy, C_1-C_6 alkylthio, thiophenyl, NH_2, Aryl (except that R^5 is other than phenyl when R^4 and Y are both hydrogen) or Heteroaryl;

R^6 is H, C_1-C_6 alkyl, benzyl, phenyl, phenyl substituted with one to five F, Cl, Br, I, NO_2, OCH_3 or C_1-C_4 alkyl; and

R^7 is H, C_1-C_6 alkyl, benzyl, phenyl, phenyl substituted with one to five F, Cl, Br, I, NO_2, OCH_3 or C_1-C_4 alkyl, or where both R^7's are taken together to form a CH_2-CH_2, CH_2-CH_2-CH_2 or CH_2-$C(CH_3)_2$-CH_2 whereby a heterocyclic ring containing the bonded P atom and the two O atoms is formed.

2. The compound of Claim 1 wherein R^2 is $-CH_2-CH(CO_2-C_1-C_6$ alkyl$)_2$, $-CH_2-CH[PO(O-C_1-C_6$ alkyl$)_2]_2$ $(C-C_3H_3)-(PO(OC_2H_5)_2)_2$ or $-CH_2$-morpholinyl.

3. The compound of Claim 2 wherein said C_1-C_6 alkyl is ethyl.

4. The compound of Claim 1 wherein R^2 is a terminal olefin substituted with a hydroxyl and $(CH_2)_m-CO_2R^6$.

5. The compound of Claim 1 wherein said R^3 is methyl.

6. The compound of Claim 1 wherein said R^4 is hydrogen, benzyloxy or hydroxyl.

7. The compound of Claim 1 wherein said R^5 is Cl, methoxy, phenyl, thiophenyl or piperidinyl.

8. The compound of Claim 1 where R^3 is methyl, R^4 is hydrogen and R^5 is phenyl.

9. The compound of Claim 8 which is

a) 4(3H)-Pyrimidinone, 2-(chloromethyl)-3-methyl-6-phenyl-;

b) 4(3H)-Pyrimidinone, 3-methyl-2-(phenoxymethyl)-6-phenyl-;

c) 4(3H)-Pyrimidinone, 3-methyl-6-phenyl-2-[(phenylthio)methyl]-;

d)Phosphonic acid, [2-(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)-ethylidene]bis-, tetraethyl ester;

e) Propanedioic acid,[(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)-methyl]-, diethyl ester;

f) 2-Pyrimidinepropanoic acid, .alpha.-(diethoxyphosphinyl)-1,6-dihydro-1-methyl-6-oxo-4-phenyl-, ethyl ester;

g) 4(3H)-Pyrimidinone, 3-methyl-2-(4-morpholinylmethyl)-6-phenyl-;

h) 4(3H)-Pyrimidinone, 3-methyl-6-phenyl-2-piperidinyl-;

i) 4(3H)-Pyrimidinone, 3-methyl-6-phenyl-2-pyrrolidinyl-;

j) 4(3H)-Pyrimidinone, 2-dimethylamino-3-methyl-6-phenyl-;

k) 4(3H)-Pyrimidinone, 2-methoxy-3-methyl-6-phenyl-;

l) 4(3H)-Pyrimidinone, 2-(aziodomethyl)-3-methyl-6-phenyl-;

m) 4(3H)-Pyrimidinone, 2-(iodomethyl)-3-methyl-6-phenyl-;

n) 4(3H)-Pyrimidinone, 2-(aminomethyl)-3-methyl-6-phenyl-;

o) Butanoic acid, 4-[[(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)

methyl]amino]-4-oxo-;

p) Pentanoic acid, 5-[[(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)methyl] amino]-5-oxo-;

q) 4(3H)-Pyrimidinone, 3-methyl-6-phenyl-2-[(phenylsulfonyl)methyl]-;

r) 4(3H)-Pyrimidinone, 3-methyl-6-phenyl-2-[(phenylsulfinyl)methyl]-;

s) 4-Pentenoic acid, 5-(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)-4-hydroxy-, (Z)-;

t) 5-Hexenoic acid, 6-(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)-5-hydroxy-, (Z)-;

u) 4-Pentenoic acid, 5-(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)-4-hydroxy-, methyl ester, (Z)-;

v) Phosphonic acid, [(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl) cyclopropylidene]bis-,tetraethyl ester;

w) Cyclopropanecarbonitrile, 2-(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)-, trans-;

x) Cyclopropanecarbonitrile, 2-(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)-, cis; or

y) Propanedioic acid, [2-(1,6-dihydro-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)-ethyl]-, bis(1,1-dimethylethyl) ester.

10. The compound of Claim 1 which is

a) 4(3H)-Pyrimidinone, 2,3-dimethyl-6-phenyl-5-(phenylmethoxy)-;

b) Phosphonic acid, [3-[1,6-dihydro-1-methyl-6-oxo-4-phenyl-5-(phenylmethoxy)-2-pyrimidinyl]propylidene]bis-, tetraethyl ester;

c) Phosphonic acid, [3-(1,6-dihydro-5-hydroxy-1-methyl-6-oxo-4-phenyl-2-pyrimidinyl)propylidene]bis-, tetraethyl ester;

d) 3-(1,6-Dihydro-4-chloro-1-methyl-6-oxo-2-pyrimidinyl)-propylidene bisphosphonic acid, tetraethyl ester;

e) 3-(1,6-Dihydro-1-methyl-6-oxo-4-phenylthio-2-pyrimidinyl)-propylidene bisphosphonic acid, tetraethyl ester; or

f) 3-(1,6-Dihydro-1-methyl-6-oxo-4-piperidinyl-2-pyrimidinyl)-propylidene bisphosphonic acid, tetraethyl ester.

11. A compound of Formula I for use in treating inflammation.

12. The use of Claim 11 wherein said compound is administered to a patient in need

thereof in an anti-inflammatory effective amount of from 0.001 mg to 1.0 gram and is administered orally, intramuscularly, intravenously, transdermally, intra-articularly, subcutaneously, or intraperitoneally.

INTERNATIONAL SEARCH REPORT

Inter..onal Application No
PCT/US 94/10571

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/36 C07D239/52 C07F9/6512 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 01198 (UPJOHN) 21 January 1993 see page 15 - page 22	1,2,9-12
P,X	EP,A,0 579 425 (ROHM AND HAAS) 19 January 1994 see the whole document	1,11,12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
11 January 1995	19. 01. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Francois, J

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ...nal Application No
PCT/US 94/10571

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